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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,720	03/03/2004	Shinn-Chih Wu	WUSH3012/EM	2654

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,720	WU ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 2-7-05 has been entered. Claims 1-27 have been canceled. Claims 28-35 have been added. Claims 28-35 are pending and under consideration.

It should be noted that examiner for the present application has been changed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 29 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "wherein **if** two expression transgenes are to be introduced into a swine embryo" in lines 1-2 of claim 29 is vague and renders the claim indefinite. It is unclear whether two expression transgenes are introduced into a swine embryo or not. The term "if" renders the claim indefinite.

The phrase "wherein said mammary gland specific promoter is bovine alpha-lactalbumin promoter" in claim 32 is vague and renders the claim indefinite. There are three phrases of "a mammary gland specific promoter" in claim 28. It is unclear which "mammary gland specific promoter" is referred to in claim 32.

3. Claim 28 recites the limitation "**the** DNA sequences" in line 4. There is insufficient antecedent basis for this limitation in the claim. Claims 29-35 depend from claim 28 but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 28-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "expression genetic insert" in claim 28 is considered new matter. The specification only discloses "expression plasmid" (e.g. specification, page 3) and the amendment filed 2-7-05 fails to specify where the support of the phrase "expression genetic insert" is located in the specification. The specification fails to provide sufficient disclosure for the phrase "expression genetic insert". Therefore, the phrase "expression genetic insert" is considered new matter. Claims 29-35 depend from claim 28.

The phrase "transplanting said embryo ... into a **synchronized recipient**" in step (c) of claim 28 is considered new matter. The specification only discloses "transferring said expression plasmid by means of gene injection and embryonic implantation" (e.g. specification, page 3) and

the amendment filed 2-7-05 fails to specify where the support of the phrase "transplanting said embryo ... into a synchronized recipient" is located in the specification. The specification fails to provide sufficient disclosure for the phrase "transplanting said embryo ... into a synchronized recipient". Therefore, the phrase "transplanting said embryo ... into a synchronized recipient" is considered new matter. Claims 29-35 depend from claim 28.

6. Claims 28-30 and 32-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a 1:1 mixture of plasmids, one comprising a mammary gland specific promoter operably linked to a trasngene encoding human clotting factor IX (hFIX) and the other comprising a mammary specific promoter operably linked to a transgene encoding porcine lactoferrin, to produce a transgenic swine whose somatic and germ cells comprise said transgenes via introducing said trasngenes into a swine embryo, does not reasonably provide enablement for a method for producing a trasngenic swine whose somatic and germ cells comprise said transgenes by using a mixture of the plasmids set forth above other than the 1:1 ratio of said plasmids via introducing said trasngenes into a swine embryo so as to produce and secrete hFIX and porcine lactoferrin in the mammary tissue of said swine and to isolate these proteins from the milk of said swine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to a method for producing a transgenic swine whose somatic and germ cells comprise a transgene wherein said method comprises: (a) constructing (i) an expression genetic insert comprising two transgenes, wherein said transgenes comprise DNA

sequences encoding human clotting factor IX (hF1X) and porcine lactoferrin, respectively, wherein both transgenes are operably linked to a mammary gland specific promoter or (ii) two expression transgenes, wherein one comprises a DNA sequence encoding hFIX operably linked to a mammary gland specific promoter, the other comprises a DNA sequence encoding porcine lactoferrin operably linked to mammary specific promoter, (b) introducing said expression transgene or transgenes into a swine embryo, (c) transplanting said embryo comprising said expression trnasgene or transgenes into a synchronized recipient, (iii) allowing the embryo to develop into a transgenic swine, wherein expression of said transgenes result in the production and secretion of hFIX and porcine lactoferrin in the mammary tissue of said swine. Claim 32 specifies the mammary gland specific promoter is bovine alpha-lactalbumin promoter. Claim 34 specifies the hFIX and porcine lactoferrin are expressed on the mammary tissue of the swine stably over lactation. Claim 35 specifies further isolation of hFIX and porcine lactoferrin from the milk.

The claims encompass using any ratio, for example, 1:100 or 1:1000, of the two expression transgenes set forth above for producing a trasngenic swine whose somatic and germ cells comprise said transgenes via introducing said trasngenes into a swine embryo so as to produce and secrete hFIX and porcine lactoferrin in the mammary tissue of said swine. The specification only disclose using 1:1 ratio of the expression transgene plasmid to produce the claimed transgenic swine, and shows the sustained expression of the hFIX and porcine lactoferrin in the milk throughout the lactation of the transgenic swine and expression of the hFIX in the milk of second, third and fourth generation of transgenic swine (specification, examples 2-3).

The specification fails to provide adequate guidance and evidence for the production of transgenic swine whose somatic and germ cells comprise transgenes by using a mixture of the plasmids set forth above other than the 1:1 ratio of said plasmids via introducing said trasngenes into a swine embryo so as to produce and secrete hFIX and porcine lactoferrin in the mammary tissue of said swine and further isolate said hFIX and porcine lactoferrin from the milk.

The level of one of ordinary skill in the art is high regarding making transgenic animal is high. The art of making transgenic animal in general was unpredictable at the time of the invention. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, and the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549). Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction).

Further, the art of recombinant protein production in the milk of transgenic animal was unpredictable at the time of the invention. Mercier et al., 1997 (Transgenic Animals: Generation and Use Ed. Houdebine, LM, p 479) teach "much progress remains to be done before routinely using transgenesis for generating farm animals producing milk for non-therapeutic use. In the present state of the art, it is difficult to predict that a construct will be functional because of insufficient knowledge on gene transcript, Pre-MRNA processing, RNA and protein stability. Integration of the microinjected transgene is aleatory resulting in highly variable levels of expression, and possible detrimental effects." (page 479, paragraph 4). For example, Palmer et al., 2003 (Transgenic Res 12(3): 283-292) teach expression of recombinant human protein C in two lines of mice homozygous for the mouse whey acidic protein/human protein C transgene, and show that homozygous females had normal growth, activity and fertility, but failed to lactate normally and were unable to raise litters. Palmer concludes that "expression of rHPC induced a lactational phenotype that involves abnormal morphological, biochemical, and functional differentiation of mammary epithelial cells" and that the basis of this phenotype "may involve secondary, rather than primary, effects of rHPC on mammary gland development." Therefore, while expression of recombinant proteins driven by a mammary promoter is well known in the art, it was not predictable at the time of the invention whether ALL proteins would be expressed, whether expression would be at a physiologically functional level, and whether elevated expression of a recombinant protein could result in a pathological state.

Additionally, the claims encompass numerous different ratios of the two different expression transgenes used to generate transgenic swine. How and whether the hFIX and porcine lactoferrin proteins are going to be expressed under those different ratios of expression

transgenes expressing these two proteins is unclear and the resulting phenotype of the transgenic swine produced would be unpredictable. Therefore, while the level of skill of an artisan practicing the claimed invention will be high, in view of the unpredictability of the state of the art of animal transgenesis in general as well as production of recombinant protein in milk of transgenic animals, one skilled in the art at the time of the invention would require specific guidance and undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and the level of one of ordinary skill that is high, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER